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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/994,468	12/19/1997	STEWART D. LYMAN	2813-L	6662

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EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	21

DATE MAILED: 04/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/994468	LYMAN ET AL	
	Examiner	Art Unit	
	GAMBEL	1644	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, ~~may a reply be~~ timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/28/01

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) 1-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☑ objected to by the Examiner. SEE PTO948

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☑ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644, Technology 1600.

2. Applicant's amendment, filed 1/28/02 (Paper No. 19), has been entered.
Claims 1-30 have been amended.

Claims 1-30 are pending and being acted upon presently.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 1/28/02 (Paper No. 19).
The rejections of record can be found in the previous Office Action (Paper No. 19).

4. The filing date of the instant claims is deemed to be the filing date of the priority application, USSN 08/243,545, filed 5/11/94, as the previous priority applications do not provide written description for "a hematopoietic cell expansion medium" and "an in vitro method for expanding hematopoietic cells comprising contacting the cell with flt3-ligand, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause expansion of the hematopoietic cells", as recited in the instant claims.

Further it is noted that priority application USSN 08/209,452 appears to the earliest priority application that provides sufficient written description for "G-CSF", "GM-CSF", "SF", "EPO", "GM-CSF/IL-3", "IL-6", "at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6".

Applicant is invited to verify that the instant claims have written support and enablement under 35 USC 112, first paragraph, for the instant claims prior to , USSN 08/243,545, filed 5/11/94.

Again, the instant claims may not have the benefit under 35 U.S.C. § 120 of all of the parent filing dates. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the a particular priority application.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

6. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

7. Upon a review of the instant application and the priority applications in conjunction with applicant's arguments, filed 1/28/02, the previous rejection under 35 U.S.C. § 112, first paragraph, written description / new matter has been withdrawn.

As pointed out above, the priority application USSN 08/209,452 appears to the earliest priority application that provides sufficient written description for "IL-6".

8. Applicant's amended claims, filed 1/28/02, have obviated the previous rejection under 35 U.S.C. § 112, second paragraph.

9. Applicant's arguments in conjunction with the Lyman Katz-type declaration under 37 C.F.R. § 1.132, filed 1/28/02, are sufficient to overcome the previous rejections under 35 U.S.C. § 102 and § 103.

10. Claims 1-8, 17-26, 29 and 30 stand rejected under 35 U.S.C. 112, first paragraph, (written description), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 1/28/02 (Paper No. 19), have been fully considered but are not found convincing essentially for the reasons of record

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

Applicant notes that the USPTO's Written Description Guidelines permit claiming variants using the "at least X % language" so long as the variant possess the specific function and submits that Example 14 of the Guidelines supports the claimed invention as it reads on "at least 80% identical to the amino acids 28-160 of SEQ ID. NO: 6" .

Applicant asserts that the specification defines the genus of flt3 ligand, including their capacity to bind the flt3 receptor and having at least 80% identity to the native flt3 ligand amino acid sequence, in the specification as filed. Applicant asserts that the specification provides procedures for making biologically active variants as well as isolating additional variants. Applicant submits that the specification provides for several assays that may be used to identify flt3 ligands. Applicant relies upon the reduction to practice of two disclosed species of human and mouse flt3 ligand as representative of the genus possess the required biological activity of flt3 ligand. Applicant submit that all of the requirements analyzed in the Written Description Guidelines have been met .

As indicated previously, the limited information provided in the specification is not deemed sufficient to reasonably convey to the skilled artisan that applicant was in possession of the broadly claimed polypeptides at the time the application was filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is relying upon certain structural and/or biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses employing any "flt3 ligand" of any "mammal", as well as "at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6" ; yet the instant specification does not provide sufficient written description as to the structural features of said "flt 3 ligand" and "80% identical flt3 ligands" and the correlation between the chemical structure and the function of the genus of "flt3 ligands". Further, it has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying a "flt3 ligand" of any "mammal" or "at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6" , encompassed by the claimed invention. There is insufficient guidance based on the reliance of limited "flt3 ligands" of mouse and human disclosed in the specification as filed to direct a person of skill in the art to select or to predict particular sequences as essential for identifying "flt3 ligands" encompassed by the claimed invention.

Furthermore, Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "flt3 ligands"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant's arguments are not found persuasive.

11. Claims 1-8, 17-26, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hemopoietic cell expansion media comprising human or mouse flt3 ligand or comprising a soluble polypeptide consisting of amino acids 28-160 of SEQ ID NO: 6 does not provide enablement for hematopoietic cell expansion media comprising flt3 ligand from species other than mouse or human or comprising a soluble polypeptide comprising an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 1/28/02 (Paper No. 19), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

Applicant argues in conjunction with various legal decisions that a patent need not teach and preferably omits what is well known in the art and the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

Applicant submits that the skilled artisan would not have to undertake undue experimentation to make and use the claimed invention because determining flt3 ligand polypeptides that are at least 80% identical to SEQ ID NO: 6 is considered routine in the art and therefore would not constitute undue experimentation.

Applicant submits the reduction to practice of two working examples of mouse and human flt3 ligand as well as direction and guidance as to how to make flt3 ligands variants that bind flt3 receptor in conjunction with known screening formats would have resulted in routine experimentation at the time the invention was made.

Applicant wishes to draw attention to parent application U.S. Patent No..5,554,512 which claims similar scope (i.e. flt3 ligand polypeptides having 80% identity) have been issued.

Each application is decided on its own merits.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any "flt3 ligand" of any "mammal" or "at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6"; yet the instant specification does not provide sufficient guidance and direction as to the structural features of said scope of "flt3 ligands" and the correlation between the chemical structure and the desired molecules or specificities. The reliance on the disclosed limited examples set forth in the specification does not support the enablement for any "flt3 ligand", encompassed by the claimed invention.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "flt3 ligands" with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "mammalian flt3 ligands" encompassed by the claimed invention.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the mouse and human flt3 ligand disclosed in the specification as filed does not appear to provide sufficient enabling support for any mammalian flt3 ligand encompassed by the claimed invention and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using "mammalian flt3 ligands", including those that are "at least 80% identical to SEQ ID NO: 6" would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant's arguments are not found persuasive.

12. Claims 1-18, 27 and 29 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9 and 10 of copending USSN 08/399,404.

Again, applicant's request for this rejection to be held in abeyance is acknowledged.

13. Applicant's arguments in conjunction with applicant's amended claims, filed 1/28/02 (Paper No. 19), have obviated the previous rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,843,423.

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
April 3, 2002